Sheikh and Examiner Spear for the interview conducted on April 6, 2004. During the interview, applicants' representative discussed the pending claims and their patentability over the disclosure contained in the cited references by Akiyama et al. and Shell et al. Examiners Spear and Sheikh agreed that the cited art does not teach applicants' invention. Accordingly, the Examiners agreed that the present claims appear to be allowable and that the outstanding rejections should be withdrawn. Further, the Examiner stated that an updated search would be conducted to verify the patentability of the present claims.

The following Response is being filed to be fully responsive to the Official Action dated December 16, 2003. The comments contained herein were discussed in the interview on April 6, 2004.

1. Rejection of Claims 1-2 and 4-47 under 35 USC §103(a)

The Official Action states that claims 1-2 and 4-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Akiyama et al. (US Patent No. 5,948,773) in view of Shell et al.

As the basis of this rejection, the Official Action states, in relevant part:

> Akiyama et al. teach a pharmaceutical formulation comprising an antibacterial substance and/or an anti-ulcer substance, in that the anti-ulcer substance is a proton pump inhibitor, wherein at least either one of them is formulated into a gastrointestinal mucosa-adherent solid preparation, which comprises a matrix containing a combination mixture of fatty acid esters,

lipids and viscogenic agents, whereby lipids include saturated fatty acids or salts thereof, higher alcohols–cetyl alcohol, stearyl alcohol, fatty acid glycerol esters (mono-, di- or triglycerides), waxes, hydrocarbons–paraffin, microcrystalline wax and phospholipids) in combination with pharmaceutically acceptable excipients (see reference column 2, line 16 through col. 3, line 67); (col. 9, line 20, through col. 13, line 59).

Akiyama, as noted above teaches various forms for administration (i.e. tablets, capsules, pills, powders, etc.) Akiyama does not teach that the active compound units are *microspheres*. One of ordinary skill in the art would be capable of determining any suitable dosage form for the delivery of drugs. Such skill is evident from the reference of Shell et al.

Shell et al. teach gastric-retentive oral drug dosage forms for the controlled release of delivery of sparingly soluble drugs, insoluble particulate matter from which drugs are released and soluble drugs rendered sparingly soluble when combined with a drug modifier, wherein the dosage forms are in the form of tablets, capsules and microparticulate systems of (proteinoid) microspheres. The dosage forms are useful for delivering drugs to treat local disorders of the stomach, such as those for eradicating Helicobacter pylori, stomach and duodenal ulcers, gastritis, esophagitis and gastric carcinoma. Suitable drugs that are delivered through these dosage forms include anti-biotics and gastric acid lowering agents, such as omeprazole.

Response

a. The Akiyama et al. reference fails to establish a *prima facie* case of obviousness

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against

the presently rejected claim.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

As discussed in the interview with the Examiners, the presently claimed invention relates to an administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the individual active compound units are microspheres. The microspheres of the presently claimed invention are composed of an acid-labile active compound and (1) at least one fatty alcohol and at least one solid paraffin, (2) at least one fatty acid ester and at least one solid paraffin, or (3) at least one triglyceride and at least one solid paraffin.

In contrast, Akiyama relates to a gastrointestinal mucosa-adherent solid preparation, which adheres to a particular site in the gastrointestinal tract. In particular, Akiyama discloses that the preparation contains polyglycerin fatty acid esters and preferably such polyglycerin fatty acid esters or lipids in combination with a viscogenic agent. The viscogenic agent is said to become viscous and adherent to the gastrointestinal tract mucosa upon exposure to water. The lipids disclosed by Akiyama comprise a myriad of different types of lipids and no specific combination of an acid-labile active compound and (1) at least one fatty alcohol and at least one solid paraffin, (2) at least one fatty acid ester and at least one solid paraffin, or (3) at least one triglyceride and at least one solid paraffin is disclosed, as is presently claimed.

Further, the Akiyama et al. reference teaches away from the presently claimed invention because Akiyama et al. are focused on a mucosa-adherent solid preparation, which has a long retention time in the gastrointestinal tract (see Abstract). In contrast, the presently claimed microspheres that are obtained have "a uniformly smooth surface, a uniform, defined delivery of active compound and, with respect to gastric passage...behavior like that of a solution is to be expected." (See page 9 of specification, second sentence from the bottom of the page). Therefore, the presently claimed subject matter is not mucosa-adherent as taught by Akiyama et al.

Further evidence that Akiyama et al. teach away from the presently pending claims is the use of an enteric coating in Example 6. Akiyama et al. teach at column 21, lines 56-57 that "the obtained granules were coated with aqueous enteric Eudragit suspension…". In contrast, the instant specification states that an "object of the invention is the provision of an administration form in which the acid-labile active compound does not have to be protected by an enteric coating." (See page 3, 3rd full paragraph).

Additionally, there is absolutely no suggestion that would motivate a person of ordinary skill in the art to pick and choose the specific lipid "solid paraffin" and a "fatty alcohol", "triglyceride" or "fatty acid ester" from the myriad of other possible lipids, fatty acids, polyglycerols, polyglycerin fatty acid esters, viscogenic agents and polymers contained in the Akiyama et al. reference to arrive at the presently claimed matrix that is not mucosa-adherent.

Accordingly, the Akiyama et al. reference fails to teach or suggest all the limitations of the claims of the present invention as required by *In re Wilson* and falls far short of beginning to establish a *prima facie* case of obviousness.

b. The Shell et al. reference does not remedy the deficiencies of the Akiyama et al. reference

The Examiner alleges that "Akiyama does not teach the active

compound in microspheres. Shell resolves this only deficiency of Akiyama by teaching a gastro-retentive formulation in the form of tablets, capsules and microspheres, wherein the drugs that are delivered through these dosage forms include proton pump inhibitors, such as omeprazole."

However, as shown above, the teaching of Akiyama is deficient with regards to teaching the presently claimed invention in many more ways than just the absence of a microsphere as a dosage form. However, even if the Akiyama et al. reference were to teach all of the features of the claimed invention except for the microsphere, the Shell et al. reference still would not remedy this deficiency because it also teaches away from the presently claimed invention.

The microspheres of the presently pending claims are composed of an acid-labile active compound and (1) at least one fatty alcohol and at least one solid paraffin, (2) at least one fatty acid ester and at least one solid paraffin, or (3) at least one triglyceride and at least one solid paraffin. The microspheres are prepared by spray drying, spray solidifying or prilling, preferably vibration prilling. (See pages 8-9 of the instant specification).

In contrast, Shell et al. teach microspheres composed of amino acids. (See column 4, line 64; column 6, lines 34-35; column 7, lines 13-15). Shell et al. do not teach microspheres composed of fatty alcohols, triglycerides or fatty acid esters and solid paraffin as required by the presently pending claims. Thus, Shell

et al. teach away from the presently pending claims.

Therefore, the combined teaching of the references of record fail to teach or suggest all the limitations of the claims of the present invention as required by *In re Wilson*. The skilled artisan would in no way be motivated to combine the teachings of Akiyama et al. and Shell et al. to arrive at the presently pending claims.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-2 and 4-47 and allow these claims to proceed to grant.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of pending claims 1-2 and 4-47. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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